

Hypertrophic Cardiomyopathy

Adenosine Monophosphate-Activated Protein Kinase Disease Mimicks Hypertrophic Cardiomyopathy and Wolff-Parkinson-White Syndrome

Natural History

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OBJECTIVES	The aim of this study was to investigate the clinical expression of adenosine monophosphate-activated protein kinase (AMPK) gene mutations (PRKAG2) in adenosine monophosphate (AMP) kinase disease based on 12 years follow-up of known mutation carriers and to define the prevalence of PRKAG2 mutations in hypertrophic cardiomyopathy (HCM).
BACKGROUND	Adenosine monophosphate-activated protein kinase gene mutations cause HCM with Wolff-Parkinson-White syndrome and conduction disease.
METHODS	Clinical evaluation of 44 patients with known AMP kinase disease was analyzed. Mutation analysis of PRKAG2 was performed by fluorescent single-strand confirmation polymorphism analysis and direct sequencing of abnormal conformers in 200 patients with HCM.
RESULTS	Only one additional mutation was identified. The mean age at clinical diagnosis in the 45 gene carriers was 24 years (median 20 years, range 9 to 55 years). Symptoms of palpitation, dyspnea, chest pain, or syncope were present in 31 (69%) gene carriers; 7 (15%) complained of myalgia and had clinical evidence of proximal myopathy. Skeletal muscle biopsy showed excess mitochondria and ragged red fibers with minimal glycogen accumulation. Disease penetrance defined by typical electrocardiogram abnormalities was 100% by age 18 years. Thirty-two of 41 adults (78%) had left ventricular hypertrophy (LVH) on echocardiography, and progressive LVH was documented during follow-up. Survival was 91% at a mean follow-up of 12.2 years. Progressive conduction disease required pacemaker implantation in 17 of 45 (38%) at a mean age of 38 years.
CONCLUSIONS	The AMP kinase disease is uncommon in HCM and is characterized by progressive conduction disease and cardiac hypertrophy and includes extracardiac manifestations such as a skeletal myopathy, consistent with a systemic metabolic storage disease. Defects in adenosine triphosphate utilization or in specific cellular substrates, rather than mere passive deposition of amylopectin, may account for these clinical features. (J Am Coll Cardiol 2005; 45:922-30) © 2005 by the American College of Cardiology Foundation

Recent reports reveal that mutations in the gene for the γ_2 subunit (PRKAG2) of adenosine monophosphate (AMP)-activated protein kinase (AMPK) may cause left ventricular hypertrophy (LVH) mimicking hypertrophic cardiomyopathy (HCM) with electrophysiologic abnormalities (including Wolff-Parkinson-White [WPW] syndrome and atrio-ventricular block) (1-3). AMP kinase acts as an enzymatic modulator of adenosine triphosphate (ATP) sensitivity to cellular energy requirements. Although murine models of AMP kinase disease have identified deposition of amylopectin in myocytes as a fundamental mechanism of disease (4),

a storage abnormality alone does not fully explain the heterogeneous nature of the disorder in man.

Hypertrophic cardiomyopathy is caused by mutations in several genes encoding sarcomeric proteins affecting the contractile apparatus of the myocardium, although a unifying molecular mechanism is still not established (5). Some studies suggest that hypertrophy develops as a consequence of compensation for impaired contractile activity, but studies of other sarcomeric gene mutations have demonstrated enhanced contractile function (6). The effects of individual mutations may be exerted at many levels other than the contractile function of individual fibers. These include disruption of sarcomere assembly, distortion of normal cellular architecture, or dysregulation of the normal feedback loops regulating the function for the intact heart. Several murine models of HCM suggest that the hypertrophic response may be due to chronic inefficiency of energy utilization by the heart. The isolation of disease-causing

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Abbreviations and Acronyms

AMP	= adenosine monophosphate
AMPK	= adenosine monophosphate-activated protein kinase
HCM	= hypertrophic cardiomyopathy
LVH	= left ventricular hypertrophy
MLVWT	= maximum left ventricular wall thickness
NYHA	= New York Heart Association
WPW	= Wolff-Parkinson-White

PRKAG2 mutations led to suggestions that defects in a central sensing mechanism handling ATP utilization might also be important in the development of hypertrophy in HCM (7). We assessed the prevalence of PRKAG2 mutations in a series of HCM probands, and in a selected cohort of 100 HCM probands with conduction disease or pre-excitation. In addition, we describe the detailed 12-year follow-up of 45 patients with AMPK disease, and define the relevance of this pathway to the wider HCM population.

METHODS

Genetic screening. We have previously identified 30 patients from two families with mutations in PRKAG2 (Asn488Ile, Family H304, and Arg302Gln, Family H363) (2). After appropriate genetic counseling and written informed consent, 94 first- and second-degree relatives of the identified probands were offered genetic screening for the identified mutations.

Mutation analysis was performed in 100 selected consecutive HCM patients and in an additional 100 HCM patients with evidence of premature sinoatrial or atrioventricular conduction disease ($n = 68$), with a short PR interval ($n = 20$), or with features consistent with an accessory pathway on the surface electrocardiogram (ECG) ($n = 12$) selected from a dedicated cardiomyopathy clinic at St. George's Hospital Medical School, London, United Kingdom, over a 12-year period, from a total HCM patient population of 1,468 patients. Deoxyribonucleic acid was extracted from whole blood as described previously (2) and then subjected to analysis using fluorescent oligonucleotide primers (Sigma-Aldrich, Gillingham, United Kingdom) complementary to flanking intron sequences for all 16 protein-encoding exons for polymerase chain reaction amplification. Primer sequences and polymerase chain reaction conditions are available on request. The resultant polymerase chain reaction product was analyzed by conventional single-strand confirmation polymorphism (standard 10% polyacrylamide gel electrophoresis in $1 \times$ Tris-Borate-EDTA buffer at room temperature and post-electrophoresis silver staining) and abnormal conformers subjected to direct sequencing using an ABI 3100 sequencer (Applied Biosystems Inc., Foster City, California). When a mutation was identified, a second blood sample from the affected patient was reanalyzed to confirm the finding by single-strand confirmation polymorphism. We have previously shown

95% sensitivity and 97% specificity compared with direct sequencing for this method in mutation screening for HCM (8).

Clinical screening. We analyzed initial and follow-up clinical data on those probands and their relatives who had mutations in the γ_2 subunit of the AMPK gene (PRKAG2). We have previously published the cardiac evaluation of 30 patients from two families and here present the broader phenotypic assessment and long-term follow-up on 45 gene carriers from three families with mutations in PRKAG2 (2,9). After written informed consent, all patients underwent standard investigative clinical assessment involving clinical history and examination, electrocardiogram, two-dimensional and Doppler echocardiographic assessment, metabolic exercise testing, and 24-h Holter monitoring with at least annual outpatient follow-up.

Ventricular pre-excitation on ECG was diagnosed on the basis of a short PR interval (<120 ms) with a widened QRS complex (>110 ms) or with an abnormal initial QRS vector (a delta wave); ECGs typical of WPW were defined by the presence of a short PR interval and a delta wave. Romhilt-Estes criteria for LVH on ECG were used (10). Sinus node disease was defined by symptomatic bradycardia at rest <50 beats/min or symptomatic chronotropic incompetence on exercise testing (11). Transthoracic two-dimensional and Doppler echocardiography was performed by a cardiomyopathy specialist in accordance with the recommendations of the American Society of Echocardiography (12). Left ventricular hypertrophy was defined where maximal septal or free wall thickness measured at least 13 mm in the absence of known acquired causes of LVH. The magnitude and distribution of LVH were assessed in the parasternal short-axis and confirmed in parasternal long-axis and apical views as previously described (13). Progression of hypertrophy was defined as an increase in maximum left ventricular wall thickness (MLVWT) >3 mm, and regression a decrease >3 mm. Impaired systolic function was defined where percent fractional shortening was $\leq 25\%$. Patients underwent exercise testing on a bicycle ergometer (Sensor-medics Ergometrics 800S, Bitz, Germany) using a ramp protocol of 10 to 15 W with respiratory gas sampling and serial measurements of blood pressure during exercise. Peak oxygen consumption was defined as the highest peak oxygen consumption achieved during exercise. Invasive electrophysiologic studies were performed when symptoms suggested sustained arrhythmias.

Full neurological assessment by a specialist neurologist was performed with clinical examination and electromyography in all patients complaining of myalgia. Open biopsy of the vastus lateralis was performed in two patients, and 8 μm -thick frozen sections were cut and stained using hematoxylin and eosin, Gomori's trichrome method, periodic acid-Schiff, and Sudan black using routine protocols. Enzyme histochemical preparations for succinic dehydrogenase, cytochrome oxidase, nicotinamide adenine dinucleotide dehydrogenase tetrazolium reductase, adenosine

triphosphatase at pH 4.2, 4.3, and 9.4, phosphorylase, acid phosphatase, and myoadenylate deaminase were made using routine methods. A small sample of muscle was fixed in glutaraldehyde and processed for electron microscopy using standard protocols. Semi-thin (1- μ m) resin sections were cut and stained using toluidine blue for light microscopy; 70 nm sections were cut, mounted on copper grids, and stained with uranyl acetate and lead citrate for electron microscopy.

Data analysis. Statistical analysis was performed using SPSS statistical software (version 10.0, SPSS Inc., Chicago, Illinois). All data are expressed as mean values \pm SD (range) or frequency (percentage). Differences between mean values were determined using the unpaired or paired Student *t* test, where appropriate. The chi-square test was used for comparisons between dichotomous variables. Survival estimates were calculated by Kaplan-Meier method.

RESULTS

Genetic results. No sequence variations in PRKAG2 were found in the first cohort of HCM patients randomly selected for mutation analysis (*n* = 100). In the second, selected cohort of HCM patients with electrophysiologic abnormalities (*n* = 100), only one additional proband was found to be carrying a PRKAG2 mutation: a missense mutation predicted to cause the amino acid substitution Arg302Gln was identified in a 30-year-old (H9.1) with HCM and WPW syndrome. He received a pacemaker at the age of 20 years after developing symptomatic atrioventricular block. Full clinical screening of his family showed no abnormalities, and the mutation was found to have arisen de novo on genetic screening and haplotype analysis of the pedigree. This mutation has been previously described by our group in four members of another unrelated family (family H363) with HCM and WPW syndrome. In family H304, we have previously reported 26 members with an Arg488Ile mutation in PRKAG2 (2). We have subsequently identified 14 additional mutation carriers from this family, who are also described here.

These two mutations are proposed to be disease-causing as they were not seen in unaffected family members, nor in 100 normal controls, and they altered residues that are conserved through evolution. In addition, prior functional studies and murine models incorporating these mutations have suggested pathogenicity (4).

Clinical results. In the 45 mutation carriers from three families in this study (Table 1), disease expression was characterized by accessory pathways on surface ECG, progressive conduction disease, and progressive LVH on echocardiography. In addition, myalgia and a proximal myopathy were documented.

INITIAL PRESENTATION. Mean age at initial presentation was 24 years (median 20 years, range 9 to 55 years). Twenty-two (48%) gene carriers had palpation, 7 (15%) had pre-syncope, and 13 (28%) syncope. At presentation, 11 (24%) had exertional dyspnea, of which 10 had New York

Table 1. Clinical Features of Individual Families With PRKAG2 Mutations

Mutation (Family)	Asn488Ile (H304)	Arg302Gln (H363)	Arg302Gln (H9)
Number affected	<i>n</i> = 40	<i>n</i> = 4	<i>n</i> = 1
Age at diagnosis (yrs)	19 (3–45)	26 (15–38)	20
Asymptomatic	14 (35%)	0	0
Syncope	5 (12.5%)	4 (100%)	1 (100%)
Myalgia	7 (18%)	0	0
Pre-excitation	23 (58%)	4 (100%)	0
AF/SVT	12 (30%)	3 (75%)	0
NSVT	3 (7.5%)	0	0
LVH by echo (adults)	28 (70%)	3 (75%)	1 (100%)
Mean MLVWT (mm)	24 (13–45)	16 (15–16)	32
PPM	12 (30%)	4 (100%)	1 (100%)
Stroke	3 (7.5%)	0	0
SCD	1	0	0
Progressive LVH (adults)	13 (57%)	0	0

AF = atrial fibrillation; echo = echocardiography; LVH = left ventricular hypertrophy; MLVWT = maximal left ventricular wall thickness; NSVT = non-sustained ventricular tachycardia; PPM = pacemaker; SCD = sudden cardiac death; SVT = supraventricular tachycardia.

Heart Association functional class 2 symptoms and 1 had class 3 symptoms. Nine patients (20%) had chest pain. Seven patients (15%) had symptoms of myalgia and or proximal muscle weakness, with calf and thigh muscle pain particularly after exercise. Four had epilepsy (including three of those with myalgia) with generalized tonic-clonic seizures poorly controlled by medication. Fourteen gene carriers (31%) were asymptomatic, at a mean age of 26 years (range 10 to 47 years).

ECG AND HOLTER AT INITIAL PRESENTATION. A short PR interval (<120 ms) was present in 30 (66%). Ventricular pre-excitation including the presence of a delta wave was identified in 27 (60%) patients; ECG criteria for LVH were present in 35 (77%) patients. Thirteen had right bundle branch block, 7 left bundle branch block, and depolarization abnormalities with a bizarre QRS configuration (Fig. 1) were noted in 17. There was 100% penetrance for ECG abnormalities (LVH with re-polarization change, abnormal QRS, short PR interval, and/or delta waves) by the age of 18 years. Sixteen (35%) patients had evidence of sinus node disease, with chronotropic incompetence on exercise testing. Thirteen (28%) patients had paroxysmal or established atrial fibrillation, and two had paroxysmal supraventricular tachycardia. There were three (6%) patients with documented non-sustained ventricular tachycardia on Holter monitoring (two with severe LVH on echocardiography >30 mm).

ECHOCARDIOGRAPHIC CHARACTERISTICS. Left ventricular hypertrophy was present in 32 of 41 patients (78%) over the age of 18 years. Of those patients with hypertrophy, mean MLVWT was 21 mm (median 18 mm, range 13 to 45 mm). The pattern of hypertrophy varied within families and within immediate kinships; 12 patients had asymmetric septal hypertrophy, 19 had concentric hypertrophy, and 1 had distal hypertrophy. The distribution of hypertrophy was often eccentric; in three patients, maximal hypertrophy was

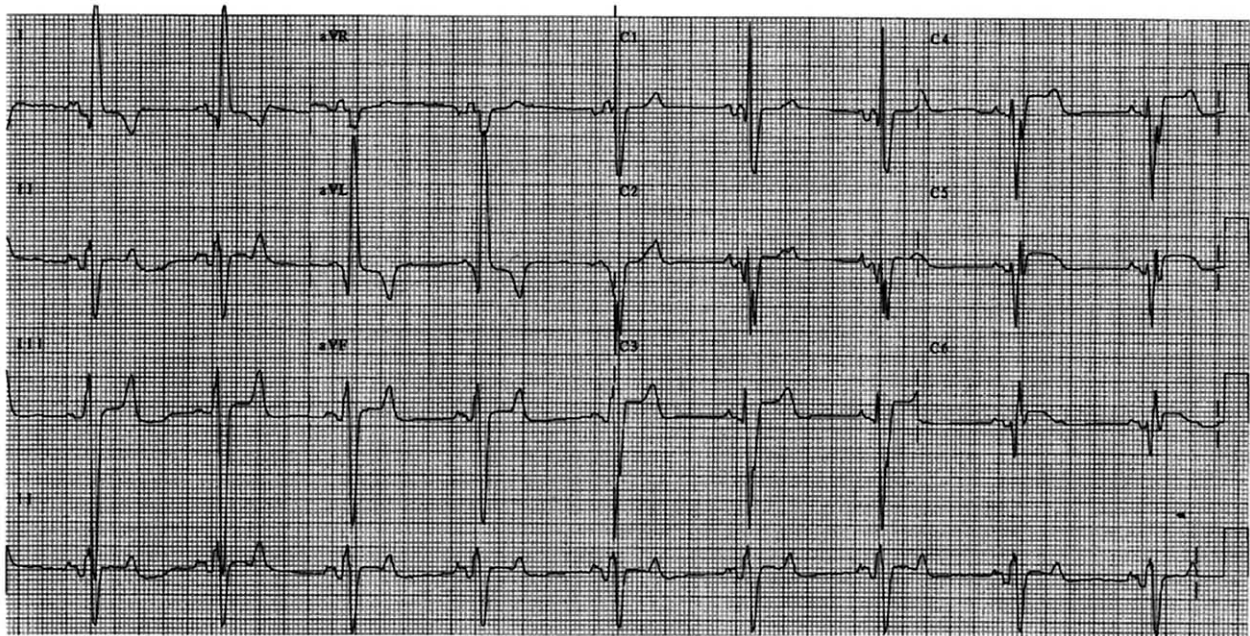


Figure 1. Electrocardiogram of a 28-year-old mutation carrier showing characteristic changes of adenosine monophosphate kinase disease: left ventricular hypertrophy by voltage, short PR interval, delta wave, and bizarre QRS configuration.

at the inferolateral wall, and in three others at the inferoposterior wall. One patient had complete systolic anterior motion of the mitral valve with left ventricular outflow tract obstruction of 65 mm Hg, another had partial systolic anterior motion of the mitral valve with no outflow tract obstruction. No other patient had systolic anterior motion of the mitral valve or a gradient >30 mm Hg. A restrictive mitral inflow Doppler pattern (E/A ratio >2.0 , DT <150 ms) was seen in 12 of 32 patients (37%). No patient had a delayed relaxation pattern. Mean left atrial diameter was 34 mm (range 21 to 54 mm). Nine of 41 subjects over the age of 18 years (22%) had normal left ventricular cavity dimensions, normal left ventricular wall thickness, and normal left atrial dimensions, at a mean age of 27 years (median 27 years, range 18 to 37 years).

EXERCISE CAPACITY. Mean percent predicted peak oxygen consumption achieved (measured in 13 patients) was 76% (range 38% to 114%). There were no exercise-induced ventricular arrhythmias. Three patients had an abnormal blood pressure response to exercise, with a failure to raise systolic blood pressure >25 mm Hg from baseline. None of these three patients had asymmetric septal hypertrophy, diastolic dysfunction by echocardiography, or LVH >15 mm.

ELECTROPHYSIOLOGIC STUDY. Eight patients underwent formal electrophysiologic study because of symptomatic sustained palpitations with a surface ECG consistent with WPW syndrome. The Wenckebach point was reduced in four patients at a mean cycle length of 520 ms, but intravenous adenosine produced atrioventricular block in only two patients. Four accessory pathways were identified, three posteroseptal, one mid-septal, with effective refractory

periods of 200 to 290 ms. No reentry tachycardias were induced. Ventricular fibrillation was induced in one patient during high right atrial pacing. Three pathways were successfully ablated by radiofrequency ablation.

SKELETAL MYOPATHY. Seven patients (15%) complained of myalgia, during or immediately after short bursts of aerobic exercise. Neurological assessment showed evidence of proximal weakness; electromyography was normal in five patients. Light microscopy of the vastus lateralis showed that muscle fibers were of normal size (40 to 90 μ m). Ragged red fibers were demonstrated throughout the biopsy using Gomori's trichrome preparation, succinic dehydrogenase, and NADH-TR and were predominantly found to be type 1 fibers. No cytochrome-oxidase-negative fibers were seen; however, the ragged red fibers were strongly stained in this preparation (Fig. 2A). Although no excess glycogen was evident on periodic-acid Schiff staining, examination of semithin sections showed that several fibers contained a mild excess of glycogen. Ultrastructural examination confirmed the presence of excess glycogen that occasionally appeared to be within mitochondria. As expected in the context of ragged red fibers on histologic analysis, increased numbers of mitochondria were found, although no mitochondrial paracrystalline inclusions were seen (Fig. 2B).

Clinical follow-up. Mean clinical follow-up was 12.2 years (median 12 years, range 1 to 41 years) with clinical examination, ECG, and echocardiographic studies repeated at approximately annual intervals. Survival at last follow-up was 91%. There were four disease-related deaths. Three died from thromboembolic strokes secondary to atrial fibrillation (at age 55, 57, and 62 years), with poor compliance

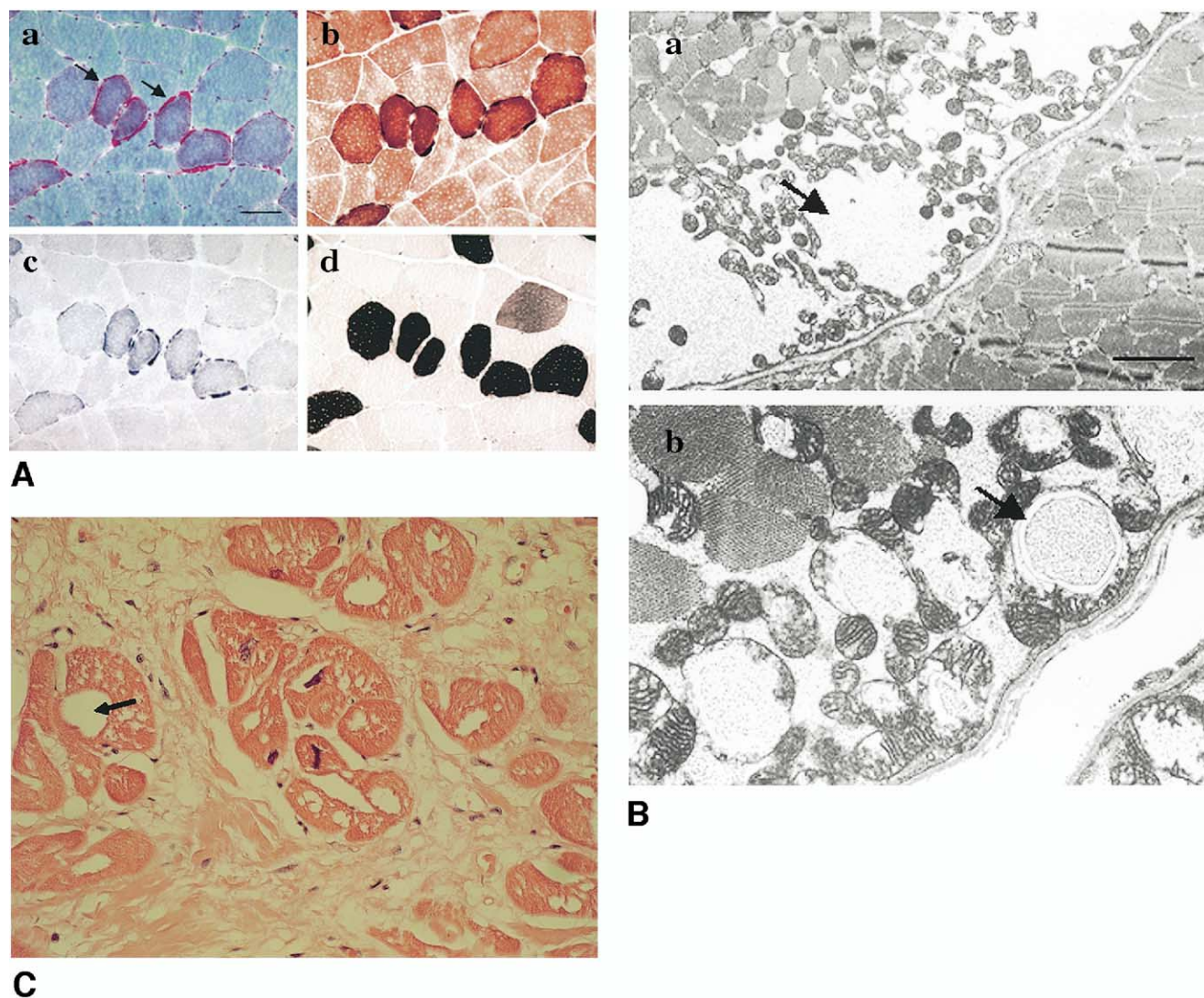


Figure 2. (A) Frozen sections of skeletal muscle showing ragged red fibers indicated by arrows (a: Gomori's trichrome) that are strongly stained in the cytochrome oxidase (b) and succinic dehydrogenase (c) preparations. Fiber typing shows that these fibers are darkly stained type 1 fibers (d: ATPase pH 4.3). Bar in panel a represents 60 μ m in panels a, b, c, and d. (B) Ultrastructural examination shows an excess of mitochondria and glycogen (arrow) at the periphery of a muscle fiber (a). Glycogen is sometimes seen within mitochondria (b, arrow). Bar in panel a represents 2 μ m in panel a and 1 μ m in panel b. (C) Histology from the postmortem myocardium of the 27-year-old patient with sudden cardiac death reveals coarse interstitial fibrosis, with extensive vacuolation of myocytes (arrow), marked pleomorphism of nuclei, and minimal disarray (H+E, \times 200). Electron microscopy showed non-specific degenerative changes in mitochondria (not shown).

with, or interruption of, anticoagulation in all three cases at time of stroke. A fourth patient died suddenly at the age of 27 years in 1994. He had massive LVH (MLVWT 45 mm) and previously documented non-sustained ventricular tachycardia. No patient underwent cardiac transplantation. There were no non-fatal strokes. Two patients with myalgia had progressive symptoms, one with decreased power requiring a wheelchair by the age of 46 years.

Twenty-four patients who were adults at time of initial evaluation exhibited significant ECG changes over time. Seven patients developed complete atrioventricular block, five developed right bundle branch block, two left bundle branch block, and two had intermittent left bundle branch block and right bundle branch block. Right bundle branch block pattern changed from rsR to Rsr in three, and an

eccentric pattern of intraventricular conduction delay >120 ms was seen in six patients. Ten developed sinus node disease with symptomatic bradycardia and/or chronotropic incompetence. New anterolateral T-wave inversion appeared in two (without development of voltage criteria for LVH on ECG). QRS axis changed from normal to left axis in three. An intermittent slurred upstroke (delta wave) was documented in two patients. Figure 3 shows a spectrum of ECG change in adults, including ECG change in the absence of echocardiographic evidence of increased hypertrophy.

By the end of the study period, 17 of the 45 patients (38%) had pacemakers implanted (Fig. 4), 7 for atrioventricular block, and 10 for symptomatic sinus bradycardia or chronotropic incompetence. Mean age of onset of symp-

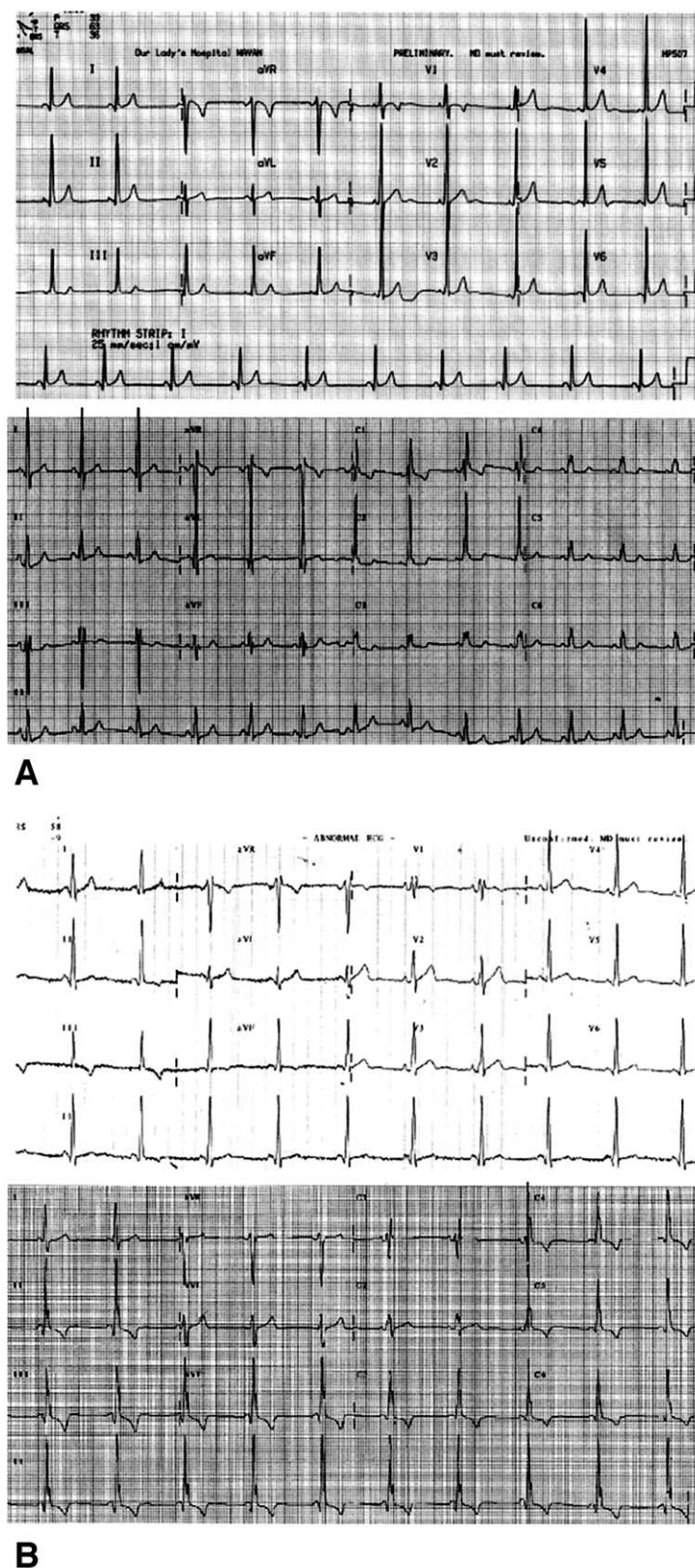


Figure 3. (A) Progressive electrocardiogram (ECG) change in adenosine monophosphate kinase disease: ECG of 19-year-old female with a short PR and left ventricular hypertrophy (**upper**) who developed a new rsR pattern and left-axis deviation by the age of 28 (**lower**). Her echocardiogram showed maximum left ventricular wall thickness (MLVWT) increasing from 14 to 17 mm. (B) Electrocardiogram of a 28-year-old female at time of initial assessment (**upper**), with an intraventricular conduction delay (IVCD) and a slurred QRS upstroke, which by age 35 years (**lower**) shows the development of a more widespread and bizarre IVCD, with diffuse T-wave inversion. This patient had no documented echocardiographic progression of disease, with MLVWT stable at 11 to 12 mm.

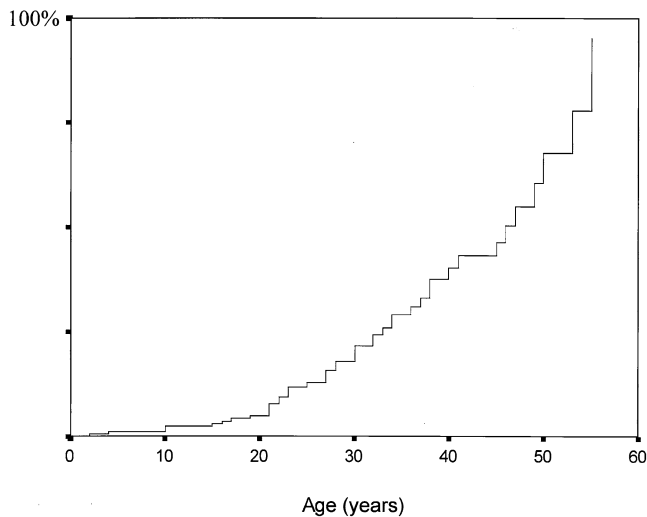


Figure 4. Relationship of age to cumulative pacemaker implantation.

tomatic conduction disease was 38 years (median 37 years, range 16 to 56 years). In three cases the development of atrioventricular block was sudden and clinically dramatic with a slow ventricular escape rhythm and causing vascular collapse requiring urgent pacing.

Implantable cardioverter defibrillators (ICDs) were implanted for primary prophylaxis in two patients (age 20 and 22 years) with massive LVH, one of whom had ventricular fibrillation during high right atrial pacing at electrophysiologic study. Neither experienced ICD discharge during a mean of 31 months follow-up.

Of the 30 adults in this study at baseline, four died, and three had no echocardiographic follow-up. Of the 23 adults assessed serially at a median of 10 years (range 7 to 12 years), 13 (57%) had progressive LVH (from a mean of 15 ± 4 mm to 20 ± 3 mm, $p = 0.002$), there was no change in 6 (26%), and regression of hypertrophy was seen in 4 (17%). Figure 5 shows change in maximal LVWT by echocardiography in adults. Five patients developed massive hypertrophy >30 mm. Two of these patients progressed to a dilated phase with wall thinning. Five patients developed impaired systolic function at follow-up with reduced percent fractional shortening <25 (mean 21%). There was no apparent effect of beta-blocker therapy ($n = 2$), angiotensin-converting enzyme inhibitor therapy ($n = 1$), or systemic hypertension ($n = 1$) on progression. No patient underwent myectomy or alcohol septal ablation.

DISCUSSION

The AMPK is a ubiquitous enzyme system that appears to act as a “fuel gauge” in cells. An increase in the AMP/ATP ratio triggers activation of the AMPK, with subsequent phosphorylation of a number of downstream targets switching off those energy (ATP)-utilizing pathways that are not essential for cell survival and switching on catabolic energy-generating pathways. PRKAG2 encodes the γ_2 regulatory subunit, but the effects of the disease-causing mutations

described in this gene on the overall activity of AMPK appear to vary with the experimental model used (14,15). The mutations are predicted to uncouple cellular metabolism to some extent from the ambient energetic needs. The deposition of a glycogen-like substance, amylopectin, in the hearts of mice overexpressing transgenic mutant PRKAG2 suggests that the cell may be inappropriately sensing a reduced ATP requirement (4). In this model, focal amylopectin deposition leads to the development of echocardiographic LVH and of accessory pathways, demonstrated to consist of bands of glycogen-filled myocytes running through the annulus fibrosis, which normally insulates the atria from ventricles (4). The myocardial histological hallmark of PRKAG2 mutations in man is widespread intracellular vacuolation and interstitial fibrosis, with deposition of amylopectin (Fig. 2C), similar to the histological appearance seen in other forms of glycogen storage disorder that mimic HCM.

The identification of disease-causing mutations in PRKAG2 led to speculation that defects in energy utilization may provide a final common pathway in the still poorly understood pathophysiology of HCM (7,16). The substantial duration of follow-up in this study provides insight into the natural history of cardiac pathology in AMPK disease. There was slowly progressive, occasionally massive, increase in wall thickness in the majority of patients followed over a mean of 12 years. In contrast, the hypertrophy in established adult sarcomeric HCM rarely progresses once established and often undergoes gradual thinning (17). However, in inherited disorders of metabolism such as Anderson-Fabry's disease and in the glycogen storage diseases the pattern of myocardial thickening also is slowly progressive (18,19). Previous studies have concentrated on the role of deposition of amylopectin as a major mechanism of disease in AMPK. However, the fact that ECG change occurred in the absence of ultrastructural or echocardiographic changes (Figs. 3A and 3B), and that skeletal muscle histology shows mitochondrial proliferation with minimal excess glycogen (Figs. 2A and 2B), suggests that deposition may not be the only mechanism of disease, and that these cellular systems might be uniquely susceptible to derangements in ATP handling. Indeed, vacuolation in the two skeletal muscle samples is remarkable by its absence. In addition, widespread coarse

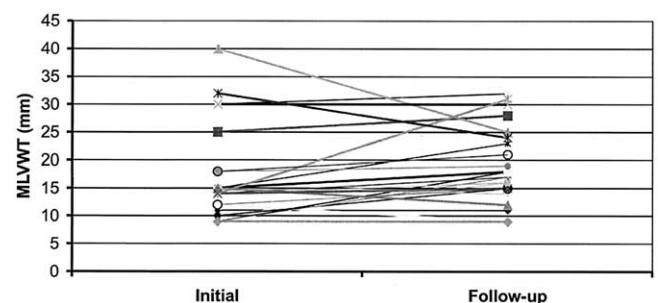


Figure 5. Change in maximum left ventricular wall thickness (MLVWT) in adults from first assessment as adults with a median follow-up of 10 years (range 7 to 12 years).

fibrosis is present in cardiac histology in this study, suggesting myocyte cell death and replacement fibrosis as seen in the context of energy mismatch in sarcomeric HCM. Thus, passive deposition of storage product is not the only mechanism of disease (4), and defects in ATP sensitivity may lead to a more widespread disruption of cellular energetics. Interestingly, there is some evidence of phenotypic heterogeneity between families. For example, all gene carriers in the two families with the Arg302Gln mutation (H9 and H363) required pacing at a mean age of 25 years. Families with the Arg531Gly mutation have associated pre-excitation, atrial fibrillation, but no reported cardiac hypertrophy (1), whereas Asn488Ile mutations are associated with cardiac hypertrophy in 78%. The Exon5:InsLeu mutation produces a phenotype dominated by cardiac failure and pre-excitation (7). Whether this phenotypic heterogeneity is a result of the specific effects of individual mutations remains to be seen. Although the molecular consequences of this defect are poorly understood, the disorder is of continuing interest in attempts to clarify mechanisms of hypertrophy in sarcomeric HCM, which may involve a response to disruption of cellular energy hemostasis (7).

This is the first systematic study of AMP kinase disease that describes a skeletal myopathy as part of the disorder. This fundamentally alters our understanding of the disease, and may help redefine it as a systemic metabolic disorder. The observation of severe myalgia and proximal skeletal myopathy highlights the extracardiac clinical manifestations of PRKAG2 mutations, and further supports the notion of a significant role for impaired energy utilization in the pathogenesis of the disorder. Analogous mutations in porcine PRKAG cause glycogen accumulation in pig skeletal muscle, which renders it commercially unusable (15). The proportion of AMPK activity in human cardiac muscle accounted for by the γ_2 subunit is more than twice the proportion provided for in skeletal muscle (20), which may account for the milder skeletal muscle clinical manifestations in vivo in this study. Importantly, this resemblance to other storage disorders involves not only skeletal muscle involvement, but also the pattern of cardiac conduction disease and ventricular pre-excitation. These mechanistic themes, coupled with the substantial clinical overlap between AMP kinase disease and primary mitochondrial disorders, suggest a common metabolic susceptibility of the normal development of the atrioventricular ring, and the cardiac conduction system. Metabolic effects have also been implicated to some extent in cardiac disease associated with lamin A/C or emerin mutations and myotonic dystrophy (21). A picture of a more fundamental disruption of cellular energetics is emerging, in which specific cellular substrates are affected by disparate genetic defects, and produce a comparable phenotype of skeletal myopathy, cardiac conduction disease, and cardiomyopathy. The relative rarity of AMP kinase disease documented in this study (albeit the screening method used is only 95% sensitive) should stimulate the ongoing search for more candidate genes in this context.

Finally, the current study suggests that the major clinical

complication of AMPK disease is progressive cardiac conduction disease, with 17 of 45 patients (38%) needing pacing by the age of 38. Accessory-pathway-mediated arrhythmias were not a major clinical feature, despite the identification of delta waves in 66% of patients. Atrial arrhythmias were common and associated with embolic stroke. Ventricular arrhythmias were infrequent and were associated with hypertrophy, and implantable cardioverter defibrillators implantation may be indicated for those with conventional HCM risk factors. The electrophysiologic characteristics of accessory pathway and atrioventricular nodal tissue were idiosyncratic: documented pathways without any inducible tachycardias, and atrioventricular block on pacing but no response to intravenous adenosine.

Conclusions. Comprehensive clinical assessment with long-term follow-up shows that AMP kinase disease is characterized by premature conduction disease requiring pacing, progressive cardiac hypertrophy, and a skeletal myopathy, consistent with a systemic metabolic storage disease. Disease-causing mutations in PRKAG2 are rare in HCM, even in the setting of complex HCM phenotypes with conduction disease and WPW syndrome. Passive deposition of amylopectin does not account for all clinical features, and further study of the effects of fundamental disruption of ATP utilization may clarify the pathophysiology of cardiac disorders with premature conduction disease and/or myopathy.

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